Remarks

Claims 1-18 were pending in the above-identified application. In response to the Examiner's indication of the finality of restriction requirement, Applicants have cancelled claims 1-6 and 8-18. By way of the present amendment, Applicants have amended claim 7, and have added new claims 19-26. Claims 7 and 19-26 are therefore currently pending and under examination. Support for the amendments to claim 7, and new claims 20-22, 25, and 26 can be found, for example, in paragraphs [0113] to [0115] and Figure 6, while support for new claim 23 can be found in paragraph [049] and support for new claims 19 and 24 can be found in paragraph [036]. Applicants respectfully request favorable reconsideration and allowance of the claims in view of the amendments and remarks provided herein.

Amendments to the Specification

Applicants have provided an amended abstract to replace the incorrect abstract that was provided in the published version of the application (Application No. 2009/0011407). The abstract published with the application appears to have been incorrectly associated with this application by the patent office, as it describes an image data correction apparatus which has nothing to do with the subject matter of the present application. The amended abstract provided herein is the same as the abstract present in WO 2005/054810, from which the current application was filed as a national stage application. Strictly speaking, this "amendment" is a correction of an error by the patent office, rather than an actual amendment by Applicants.

The Examiner objected to the disclosure for containing embedded hyperlinks in paragraph [0062], which became paragraph [0064] in the published application (Application No. 20090011407). Applicants have amended paragraph [0064] to remove the hyperlinks objected to the Examiner, and respectfully request that the objection to the specification be withdrawn.

Amendments to the Sequence Listing, and Statement Regarding the Sequence Listing

The Examiner indicated that the application fails to comply with the requirements of 37 CFR §1.821-25 because the previously submitted sequence listing did not include each of the

sequences set forth in the application. Applicants have amended the specification to provide SEQ ID NOs for all sequences present in the application. In addition, in accordance with 37 CFR §1.825, Applicants submit herewith a substitute amended paper copy of the Sequence Listing (provided as a .pdf file) as well as a computer readable form of the substitute amended Sequence Listing (provided as a .txt file). Applicants further declare that the Sequence Listing in the paper copy and the computer readable Sequence Listing are the same, and that the sequences contained in the Sequence Listings are found in the application as originally filed and therefore add no new matter to the application. Applicants submit that the application now complies with the requirements of 37 CFR §1.821-25.

Claim Rejections under 35 U.S.C. §112, 2nd paragraph

The Examiner has rejected claim 7 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse the rejection. Nonetheless, Applicants have amended claim 7 in response to the Examiner's concerns, and respectfully request that rejection of claim 7 under 35 U.S.C. §112, 2nd paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. §112, 1st paragraph

The Examiner has also rejected claim 7 under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement. In support of the assertion of lack of enablement, the Examiner has evaluated the factors described in *In re Wands*. The central question for determining if claims are enabled is whether or not the specification teaches those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Applicants respectfully assert that the present specification satisfies that requirement with regard to the claims, as amended, and respectfully traverse the rejection.

The first aspect of an enablement analysis involves determining the breadth of the claims. With regard to the breadth of the claims, Applicants have amended the claims to recite only

human individuals, and have removed the language reciting "sequences corresponding to SEQ ID NO:1", which the Examiner indicated was unclear and subject to broad interpretation.

The second aspect of an enablement analysis involves determining whether sufficient guidance has been provided to practice the invention over the full scope of the claims. Applicants assert that the specification provides sufficient guidance to make and use the claimed invention over the scope of the claims. This can be demonstrated by evaluating each of the steps of independent claim 7, and related independent claim 22.

The first step of the claimed method recites obtaining a sample that includes the 3'-untranslated region of a first human individual's CD24 gene. Applicants have provided substantial support for obtaining a sample including the genetic material to be assessed in the detailed description and examples (e.g., paragraphs [048]), which indicates that convenient tissue samples include whole blood, semen, saliva, tears, urine, fecal material, sweat, skin, and hair. Obtaining a sample including genetic material, such as the CD24 gene, is well known to those skilled in the art. Furthermore, the Examiner has not indicated that support is not present for carrying out this step. Accordingly, in view of these observations and the presumption that a patent is enabling, Applicants conclude that the first step of the claimed method is fully enabled by the specification.

The second step of the claimed method recites analyzing the sample to determine if the first human individual's CD24 gene includes deletions at positions 1580 and 1581, in view of SEQ ID NO: 1, or includes the $CD24^{1580del}$ allele. Methods for carrying out this step are again fully described in the specification. See for example paragraphs [044] to [068], which describe (in detail) the use of cell surface expression of CD24, allele specific probes, tiling arrays, allele-specific primers, direct sequencing, and denaturing gradient gel electrophoresis for identifying polymorphisms in CD24. While the Examiner asserted that this step of the claim might not be enabled for non-human species and numerous variants of CD24, Applicants have amended the claims to address the Examiner's concerns. Specifically, Applicants have amended the claims to recite only human individuals, and only the CD24 gene, rather than sequences corresponding to SEQ ID NO:1. Accordingly, Applicants conclude that the second step of the method is fully

enabled by the specification for one skilled in the art.

The third and final step of the claimed method recites determining that a first individual that is homozygous or heterozygous for the $CD24^{1580del}$ allele, or includes the corresponding deletions at positions 1580 and 1581, has a lesser likelihood of experiencing rapid progression of multiple sclerosis than a second human individual diagnosed with multiple sclerosis who is homozygous for the $CD24^{1580TG}$ allele. Methods of correlating multiple sclerosis symptoms with single nucleotide polymorphism analyses are thoroughly described in paragraphs [0073] to [0081] of the specification. However, this step of the claim appears to have prompted the majority of the Examiner's concerns, which are therefore addressed more specifically below.

The Examiner refers to the post-filing date references of Wang *et al.*, which indicated that multiple sclerosis (MS) patients with the TG/del or del/del genotype had a more delayed disease progression compared with MS patients with the TG/TG genotype. Applicants note that the reference by Wang *et al.* was co-authored Dr. Yang Liu, the first named inventor of the present application. Applicants have amended the claims, which were inadvertently drafted to recite a greater rather than lesser likelihood of rapid progression of MS. Support for the amended claim, in which and indivisual with deletions at positions 1580 and 1581 in at least one allele of the individual's CD24 gene has a lesser likelihood of experiencing rapid progression of multiple sclerosis, can be found in Figure 6, which the Examiner has indicated shows a correlation between subjects homozygous for the deletion with longer survival. Accordingly, in view of Applicants amendments to the claim, there should no longer be any significant inconsistency between the claim and the conclusions of Wang *et al.*

The Examiner also referred to the work by Gonzalez (Neurology, 2009), which appeared to run counter to the teachings of Wang *et al.* However, a close reading of Gonzalez reveals that they were investigating a somewhat different problem from that being evaluated by Wang *et al.* Gonzales evaluated the association of P1527 polymorphism with multiple sclerosis by comparing the amount of this polymorphism between individuals that have MS with the amount of this polymorphism in individuals (controls) that do not have MS. There results, using a relatively small sample size, did not show a correlation between P1527 polymorphism and MS.

However, there is a significant difference between determining a correlation with having MS, as evaluated by Gonzalez, and the risk of progression in an individual already having MS, as evaluated and claimed by the present inventors. Accordingly, there is no contradiction between the findings of Gonzalez and the findings of Wang *et al.*, or for that matter the present claim by Applicants.

The Examiner also indicated that the data provided in the specification appeared to only show a correlation with survival time, not the time period that occurred before an individual reaches EDSS 6.0. Applicants respectfully disagree, and direct the Examiner's attention to Example 7 (paragraphs [0013] and [0014]). Example 7 states that "Survival analysis revealed that SNP at 1580 have significant impact for the progression of MS." (emphasis added). The example further states that "As shown in Fig. 6, the genotypes at this position associate with the time span from the day of first MS-like symptoms to the day when the patients require walking aid." Requiring walking aid essentially defines stage EDSS 6.0 of multiple sclerosis. Accordingly, the data provided in the specification fully support the claim for an individual that is homozygous or heterozygous for the $CD24^{1580del}$ allele (or the corresponding deletions at positions 1580 and 1581) having a lesser likelihood of experiencing rapid progression of multiple sclerosis.

The Examiner also objected to apparently inconsistent results in Figure 6, asserting that since a p value greater than 0.05 is generally not considered to be statistically significant, the figure appears to indicate only that individuals heterozygous for the deletion show a correlation with longer survival. Applicants respectfully disagree. At the outset, the graph visually demonstrates that one, and then two deletions provide an increasingly protective effect against the progression of multiple sclerosis. In statistical term, there are two types of errors in interpreting p values. A Type II error equates a lack of statistical significance to a lack of difference. In Applicants' case, the higher p value was due to the low sample numbers available for the del/del group. As indicated in the top line in Fig. 6, del/del patients show a higher proportion surviving than TG/TG and TG/del patients. The somewhat >0.05 p value was due to the fact that del/del genotype is so rare that only a total of 4 cases in MS patients (including both

family cohort and case control cohort, which is visible in Fig. 6 as the number of points attributed to the genotype) were available when this study was carried out. In the log-rank test that considered all three genotypes, the p value is smaller than all pair-wise comparison. This can occur only if the del/del *vs* TG/del, del/del *vs* TG/TG and the TG/del *vs* TG/TG shown the same trends. For this reason, one can conclude that both del/del (homozygous) and del/TG (heterozygous) genotypes are protective (i.e., correlated with a lesser likelihood of rapid progression of MS). Accordingly, the data support the scope of the amended claim, which encompasses both homozygrous and heterozygous deletions.

With regard to the asserted unpredictability of the art, the Examiner has indicated that gene association studies are often unreliable at the time of their first publication. However, this does not indicate a lack of enablement if the additional work required to confirm the initial results can be characterized as routine, rather than undue experimentation. Applicants further assert that additional studies can and have been carried out in this case, using the methods described in the application, and that the subsequent studies using the described methods would be routine rather than undue. These subsequent studies have already provided confirmation of the inventors initial results by way of Wang *et al.*, referenced by the Examiner. Wang *et al.* expanded upon the initial study by using a larger population of individuals to support their results, and also proposed a mechanism through which the deletions could slow progression of MS by modulating CD24 mRNA stability.

Accordingly, for the reasons provided above, Applicants conclude that the third and final step of the method is fully enabled for one skilled in the art as well. The factors of *In re* Wands should be weighed together to determine whether or not the claims at issue are enabled, and Applicants submit that the amendments and arguments provided herein substantially shift the weight of these factors in favor of claim 7, and its dependent claims, being enabled. Because all three steps of the method are enabled for the reasons provided above, Applicants respectfully request that the rejection of claim 7 under 35 U.S.C. §112, first paragraph, for lack of enablement, be withdrawn.

In light of the foregoing, it is respectfully submitted that the present application is in

condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application. If there are any fees resulting from this communication, please charge such fees to our Deposit Account No. 03-0172.

Respectfully submitted,

Date: October 16, 2009

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